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Mini review

The role of cholesterol in prostatic diseases☆

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ABSTRACT

Cholesterol is a neutral lipid that plays an essential role in the maintenance of the integrity of biologic membranes and serves as a precursor in the synthesis of many endocrine mediators. It is also synthesized in mammalian cells via the mevalonate pathway. Recent clinical and basic research evidence has demonstrated a possible linkage of cholesterol to two of the most common diseases of the human prostate: prostatic cancer and benign prostatic hyperplasia. Accumulation of cholesterol within the lipid raft component of the cellular plasma membrane may stimulate signaling pathways that promote prostate tumor growth and progression. In addition, cholesterol-lowering drugs, such as statins, have exhibited some promising results for these prostatic diseases. This new area of research may provide insight into the underlying cellular mechanisms leading to prostate hyperplasia, prostate cancer progression, and potentially novel targets for therapeutic interventions.

1. Introduction

More than a century ago, it was reported that crystals of cholesterol and other fatty acids accumulate in solid tumors.[1] Nearly 70 years ago, Swyer demonstrated an increase in the cholesterol content in prostate adenomas compared with normal prostatic tissues.[2] Since then, studies of human subjects and animal models support the existence of a relationship between cholesterol in prostate tissues and secretions with benign and malignant prostatic neoplasms.[3] More recently, epidemiologic evidence suggests that the modern Western diet, which contains substantial levels of cholesterol and other fatty substances, promotes prostate cancer progression.[4,5] Consistent with this idea, prolonged inhibition of the cholesterol synthesis pathway by pharmacologic intervention is associated with a reduction in risk of advanced prostate cancer.[6,7] In addition, epidemiologic and clinical studies have found positive correlations between a hypercholesterolemic state and lower urinary tract symptoms (LUTS) that are suggestive of benign prostatic hyperplasia (BPH).[8,9] Therefore, the possible underlying pathophysiologic mechanisms linking cholesterol and prostatic diseases have currently become an active area of scientific research.

Cells maintain their normal structure and function by appropriately responding to changes in the surrounding environment. Transduction of extracellular stimuli is effected from the surface through the plasma membrane by a complex series of interactions among ligands, receptors, and intracellular signaling mediators. Cholesterol-enriched membrane microdomains, commonly referred to as lipid rafts, exist within the lipid bilayer of all mammalian cells, and they play important roles in signaling from the cell surface to intracellular pathways. Evidence has implicated the involvement of lipid rafts in tumor growth and aggressiveness,[10] so cholesterol-lowering treatments may be a promising therapeutic modality for prostate cancer and LUTS/BPH. This review summarizes the current supporting scientific evidence and explains the links between cholesterol with two of the most important prostate diseases: prostatic cancer and LUTS/BPH.

2. Cholesterol metabolism

Cholesterol is a prominent component in Western diets. It is a neutral lipid that plays an essential role in maintaining the integrity of biologic membranes and also serves as a precursor in the synthesis of bile acids and many endocrine signaling mediators (e.g., steroidal hormones). Apart from extrinsic sources, cholesterol is also synthesized in mammalian cells via the mevalonate pathway (Figure 1). This pathway also produces a number of other important metabolic products. For example, isoprene units are precursors in the synthesis of a variety of molecules, including proteins. Isoprenoid modification of signaling proteins, such as the Ras and Rho family members, are essential for proper membrane targeting of these molecules. Isoprenylated proteins participate in signal transduction pathways that regulate diverse processes such as the cell cycle, cell survival mechanisms, and cell motility. Therefore,

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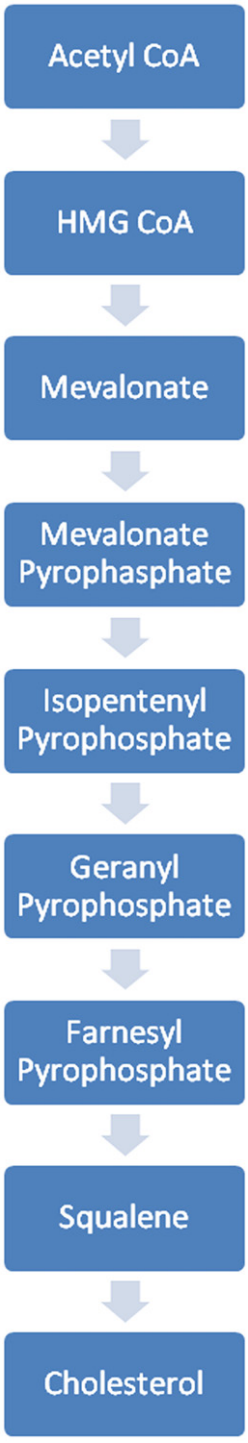

Figure 1. The mevalonate pathway in the mammalian cell. CoA = coenzyme A; HMG = 3-hydroxy-3-methylglutaryl.

mevalonate products are essential for a wide range of biologic activities, from hormonal regulation of endocrine target organs to electron transport. The complexity of products originating from the mevalonate pathway has confounded studies that focus on potential relationships between circulating cholesterol levels and prostate cancer incidence or progression, making the results difficult to interpret.[3,10]

Similar to cells in other tissues, prostatic cells endogenously synthesize cholesterol via the mevalonate pathway. Interestingly, the prostate is known to synthesize cholesterol at a rate even higher than that of the liver.[11] However, much of the cholesterol residing in cell membranes originates from the uptake of circulating lipoproteins.[12] Consequently, the cellular cholesterol content is a balance between metabolic mechanisms intrinsic to the cell and regulatory functions of cholesterol's distribution in an organism. The cholesterol content of cell membranes is under tight homeostatic regulation, and it involves synthetic pathways in the endoplasmic reticulum, transfer of cholesterol from lipoproteins to the exoplasmic leaflet, receptor-mediated internalization, several intracellular transport mechanisms, and extensive efflux from the cell via secretion of lipoprotein complexes. Evidence shows that this complex homeostatic mechanism breaks down in cancer as well as in the aging prostate.[3]

3. Evidence connecting hypercholesterolemia and LUTS/BPH

It is well recognized that obesity is a risk factor for the development of LUTS.[13] Clinical evidence shows its association with stress urinary incontinence and an overactive bladder.[14,15] In a recent report by the Third National Health and Nutrition Examination Survey (NHANES III), positive correlations were demonstrated between markers of metabolic syndrome and LUTS/BPH.[9,16] Men classified as having three or more components of metabolic syndrome had increased odds for LUTS/BPH [odds ratio (OR): 1.80; 95% confidence interval (CI): 1.11–2.94]. Besides the NHANES III report, previous clinical observations have also shown a positive correlation between metabolic syndrome and the prostate. Hammarsten and Hogstedt showed that fast-growing BPH is a risk factor for type 2 diabetes, hypertension, obesity, hypercholesterolemia, and hyperinsulinemia.[8,17] Although BPH is the most common benign neoplasm in men, its etiology remains unknown. Therefore, clinical and epidemiologic evidence of a positive correlation between LUTS/BPH and metabolic syndrome may shed some light on the etiology of BPH.

In our ongoing studies, we are investigating structural and functional changes in the prostate associated with metabolic syndrome using an animal model of fructose-fed rats (Figure 2). After receiving a high fructose diet for 2–3 months, the rats acquire a metabolic syndrome profile of obesity, insulin resistance, and hypercholesterolemia.[18,19] Preliminary data have shown that the weight of the prostate significantly increases in these rats compared with those in control rats. Histology suggests glandular

Figure 2. Age-matched male fructose-fed and control Wistar rats.

hyperplasia of the prostate from fructose-fed rats. Our results are similar to those reported by Vikram et al. in a study using rats who were fed a high-fat diet.[20] Prostatic enlargement was observed in those rats. A significant increase in cell proliferation markers confirmed the occurrence of cellular hyperplasia of the prostate. Enhanced alpha-adrenoceptor-mediated contractions in the prostate indicate augmented contractility of the gland. Taken together, both human and animal studies offer supportive evidence for a possible link between hypercholesterolemia and the occurrence of LUTS/BPH.

4. Epidemiologic studies on the relationship between cholesterol and prostate cancer

Lifestyle factors play significant roles in the clinical aggressiveness of prostate cancer. Immigrants to the United States and other Western nations from Asian countries, where the incidence of clinical prostate cancer has been low, show a dramatic increase in clinical prostate cancer.[4] This increase in cancer incidence is related to the time of arrival, with increased cancer risk associated with early arrival compared with individuals who migrated later in life.[21] Because autopsy studies have shown that the incidence of occult prostate cancer is similar in Asian and Western societies,[22,23] studies on immigrants point to an important role of extrinsic factors, such as diet, in prostate cancer progression. Michaud and colleagues examined the association of diet and prostate cancer risk in 51,529 men who contributed detailed dietary data; 1,897 total cases of prostate cancer (excluding stage A1) and 249 metastatic cancers were identified.[24] Their study concluded that the intake of red meat and dairy products is related to an increased risk of metastatic prostate cancer. Although known nutrients such as calcium and fatty acids may explain most of the dairy association observed, it appears that a portion of the risk of metastatic prostate cancer associated with red meat intake remains unexplained.

Many epidemiologic studies have not shown an association between circulating cholesterol levels and cancer risk.[25–28] However, some studies have reported statistically significant correlations between cholesterol intake and cancer risk.[29–31] Those findings are consistent with the possibility that prolonged consumption of cholesterol-rich foods might promote the progression of certain cancer types or cancer growth in selected tissues. In contrast, there are also studies reporting an inverse association between cancer incidence and cholesterol levels for certain neoplasms.[32–34] Evidence suggests that this negative relationship is probably attributable in many cases to the hypocholesterolemic effects of preexisting cancer.[35,36] Such a negative association resulted in studies being designed to identify potential cancer risks for patients on cholesterol-lowering therapy for cardiovascular disease. The results of several studies indicated that treatments for hypercholesterolemia do not increase cancer risk[37] and may even lower cancer incidence.[38] The Scandinavian Simvastatin Survival Study examined the long-term effects of simvastatin for up to 8 years on cause-specific mortality in patients with coronary heart disease. The total number of cancer deaths was 68 (3.1%) in the placebo group and 52 (2.3%) in the simvastatin group [relative risk (RR), 0.73; 95% CI, 0.05–0.51; $p = 0.087$), and numbers of noncardiovascular and other deaths were similar in the two groups.[39]

5. Cholesterol and cancer cells

Cancer cells *de novo* synthesize large amounts of fatty acids and cholesterol irrespective of circulating lipid levels, and they benefit from this increased lipid synthesis in terms of growth advantage, self-survival, and drug resistance. Possible mechanisms for the increase in cholesterol in tumors include: (1) increased absorption from the circulation[40,41]; (2) downregulation of low density lipoprotein (LDL) receptors[42]; (3) upregulation of the mevalonate pathway, particularly 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase[42,43]; and (4) direct androgen stimulation of lipogenesis in human prostate cancer cells by increasing transcription of the fatty acid synthase and HMG-CoA reductase genes.[44]

Key lipogenic alterations that commonly occur in prostate cancer include overexpression of the enzyme, fatty acid synthase, and deregulation of 5-AMP-activated protein kinase.[45] Fatty acid synthase is a key metabolic enzyme that catalyzes the synthesis of palmitate from the *de novo* condensation of malonyl-CoA and acetyl-CoA, and it plays a central role in energy homeostasis by converting excess carbon intake into fatty acids for storage. The 5-AMP-activated protein kinase functions as a central metabolic switch that governs glucose and lipid metabolism. Recent interest has focused on the potential of targeting metabolic pathways that are altered during prostate tumorigenesis and progression. Several small-molecule inhibitors of fatty acid synthase have been described or are in development for therapeutic use. In addition, drugs that directly or indirectly induce 5-AMP-activated protein kinase activation have potential benefits in prostate cancer prevention and treatment.[45]

Metastasis to the bone is one clinically important feature of prostate cancer. Current diagnostic methods cannot predict metastatic prostate cancer at a curable stage of the disease. Therefore, identification of metabolic pathways involved in the growth of bone metastases has the potential to improve prostate cancer prognoses. In a study using metabolomics to study prostate cancer, significant differences were found among bone metastases from prostate cancer, bone metastases of other cancers, and normal bone.[46] Among metabolites in the bone metastases of prostate cancer, cholesterol was especially noted. The cholesterol level in prostate cancer bone metastases was significantly increased (127.30 mg/g vs. 81.06 and 35.85 mg/g in bone metastases of other origins and normal bone, respectively). Immunohistochemical staining of prostate cancer bone metastases showed intense staining of the LDL receptor and variable levels of scavenger receptor class B type 1 and HMG-CoA reductase in tumor epithelial cells, indicating the possibility of the influx and *de novo* synthesis of cholesterol.[46]

6. Cholesterol-lowering treatments for BPH and prostate cancer

Several studies have reported regression induced in dog and rodent prostates by hypocholesterolemic agents such as the polyene macrolide candicidin.[47,48] Human trials with oral candicidin for BPH in the 1970s reported symptomatic improvement.[49,50] Patients receiving 300 mg/day of candicidin orally showed improved subjective symptoms in 89.3% of cases compared with 18.2% in patients treated with a placebo. Residual urine decreased in 85.7%, and the flow rate improved in more than 89% of cases. More than one-third of patients treated with candicidin showed an improvement in prostate size compared with none of the patients treated with the placebo.[50] However, in spite of initial encouraging results, the treatment never became popular because of a lack of long-term effectiveness.

Attempts to use epidemiologic tools to assess any potential association of dietary or circulating cholesterol with the risk of clinical prostate cancer were confronted with significant challenges. Another approach is to determine whether long-term treatment with cholesterol-lowering drugs affect the incidence and aggressiveness of prostate cancer. HMG-CoA reductase

inhibitors are cholesterol-lowering drugs that have been widely used for many years to treat cardiovascular diseases. HMG-CoA reductase catalyzes the rate-limiting step in the mevalonate pathway, and these agents lower cholesterol by inhibiting its synthesis in the liver and peripheral tissues. The possible anticancer efficacy of statins compared with other methods of lowering cholesterol may be because these agents lower serum cholesterol and reduce cholesterol synthesis in peripheral tissues and liver. This may be of considerable benefit in the case of prostatic neoplasms because the prostate is reported to synthesize cholesterol at a rate even higher than that in the liver.[11] HMG-CoA-reductase inhibitors have been demonstrated to exert potent anticancer effects in model systems. Studies with cell culture models indicated that statin drugs can inhibit cancer cell growth and motility, induce apoptosis, and inhibit endothelial cell migration and tube formation, which are properties associated with angiogenesis.[3] Mevastatin, for example, was shown to inhibit cell cycle progression in PC-3 human PCa cells by inhibiting cyclin-dependent kinase (cdk)2 phosphorylation.[51] Animal studies have verified that this class of agents has a substantial capability to retard tumor growth, *in vivo* angiogenesis, and tumor metastasis.[52] In general, statins also exhibit a robust selectivity for tumor cells over normal cells, an essential attribute for successful cancer therapy.[53] Their ability to enhance the efficacy of conventional chemotherapeutic agents has also been demonstrated.[54]

Graaf et al. examined 20,000 patients and compared those taking statins with those taking other cardiovascular-protective drugs from 1983 to 1998.[6] Those investigators found a 20% reduction in total cancer incidence in the statin cohort, with the largest reductions in the incidence of prostate and kidney cancers. Patients who terminated statin therapy returned to a baseline level of risk within 6 months.

Results of the National Health and Nutrition Examination Survey[9] showed that statin users had a nonstatistically significantly lower prostate-specific antigen (PSA) than nonusers (0.90 vs. 0.95 ng/mL; $p = 0.22$), especially in men without comorbidities ($n = 1680$; 0.86 vs. 0.99 ng/mL; $P = 0.02$). In men with comorbidities, statin users had a nonstatistically significantly higher PSA than nonusers (0.91 vs. 0.83 ng/mL; $p = 0.14$). Men with lower cholesterol had lower PSA (bottom vs. top quintile: 0.92 vs. 1.02 ng/mL; p trend = 0.06). This study concluded that statin users and men with lower cholesterol may have lower PSA. If this is the case, the probability of detecting asymptomatic prostate cancer might be lower at present, but these cases might be more likely to be diagnosed at an advanced stage in the future. Therefore, PSA-associated bias is unlikely to explain the inverse association of statins with advanced prostate cancer.[55]

Statin drugs (e.g., pravastatin, lovastatin, and simvastatin) currently have a sufficiently long clinical history so that safety concerns for many of them can be definitively evaluated. Because most statins are now known to be well tolerated by patients, continued evaluation of these compounds in clinical trials as potential chemopreventive agents or as adjuvants to standard therapy is warranted. However, generalization of the anticancer effectiveness of statins as a group is not advised, because the different compounds can exhibit significantly different activity profiles against tumor cells.[53]

7. Cholesterol and lipid rafts

In plasma membranes and other intracellular membranes, cholesterol accumulates in specialized structures known by various names, such as lipid rafts, detergent-resistant membrane domains, and detergent-insoluble, glycolipid-enriched complexes. Lipid rafts are 10–200-nm sphingolipid-cholesterol-rich microdomains (Figure 3) that compartmentalize cellular processes and can be stabilized to form larger protein–protein and protein–lipid aggregates.[56] The stability of rafts is conferred by favorable molecular interactions between sphingolipids and cholesterol. Rafts are proposed to serve as platforms to facilitate cellular signaling, viral entry, cell–cell communication, receptor down-regulation and recycling, and targeted export of proteins and lipids.[57,58] At least two morphologically distinguishable varieties of lipid rafts exist on cell surfaces. The more familiar type is named caveolae, and these are identifiable in electron micrographs as striated 50–100-nm invaginations in the plasma membrane.[59] Caveolins (caveolin-1, -2, and -3) are structural proteins that bind cholesterol and are necessary for caveolar formation. The

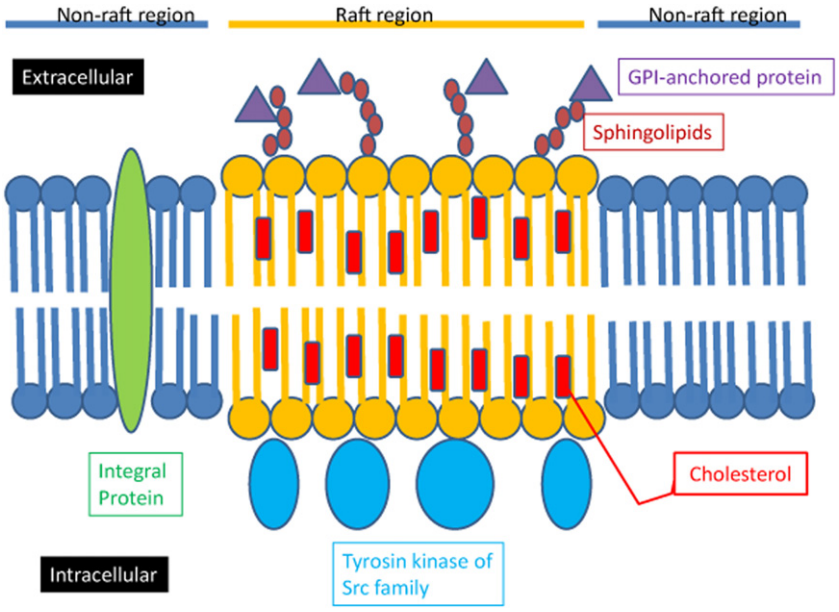

Figure 3. Model of a lipid raft. Cholesterol and sphingolipids (sphingomyelin and glycosphingolipids) are packed together to form a microdomain. The lipid raft is coated with GPI-anchored proteins on the external surface. Acylated proteins, such as tyrosine kinases of the Src family, are attached to the cytoplasmic surface. GPI = glycosylphosphatidylinositol.

second variety of raft is named the flat raft or G domain. Flat rafts do not contain caveolin proteins and therefore do not form a recognizable membrane structure identifiable on electron microscopy. Both types of lipid rafts can be biochemically isolated using similar approaches and have been shown to contain glycosylphosphatidylinositol-anchored proteins, Src family kinases, heterotrimeric G protein subunits, and other cell-signaling molecules (e.g., receptor tyrosine kinases).[60,61]

The first evidence that linked lipid rafts to prostate cancer was the identification of caveolin-1 as a marker for aggressive prostate cancer.[62,63] Subsequent studies have indicated caveolin-1 as a predictor of poor outcomes following surgery in patients with lymph node-negative prostate cancer.[64] Anticaveolin-1 antibodies have been demonstrated to suppress prostate cancer metastasis in mice, suggesting that caveolin-1 may play a direct role in metastatic dissemination.[62] Caveolin-1 has also been shown to directly interact with the androgen receptor and appears to be capable of participating in mediating androgen-dependent signals in prostate cancer cells.[65] Those findings suggest the possibility that lipid rafts may regulate prostate cancer cell growth and survival functions by compartmentalizing signaling proteins involved in hormonally responsive or dependent pathways.

Indeed, an emerging area of research is the modification of lipid rafts, which appears to have implications for human health and disease. Historically, an understanding of how changes in lipid raft organization alter cellular activity came from cholesterol-depletion studies. Recently, dietary cholesterol was found to influence lipid raft organization, with consequences of alterations in cellular functions. Future research will hopefully advance our understanding of how dietary components can affect cellular functions through lipid rafts.

8. Conclusions

Recent clinical and basic research evidence demonstrates a possible link of cholesterol to two of the most common diseases of the human prostate: prostatic cancer and BPH. Accumulation of cholesterol within the lipid raft component of cellular plasma membranes may stimulate signaling pathways that promote prostate tumor growth and progression. This new area of research may provide insights into the underlying cellular mechanisms leading to prostatic hyperplasia, prostate cancer progression, and potentially novel targets for therapeutic interventions.

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